--27.(2x amended) A method of treating a malignant tumor in a subject wherein the malignant tumor comprises tumor cells around which tenascin has been deposited, which comprises administering to the subject an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells, wherein the agent is an antibody, a peptide or a peptidomimetic in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin so that the leukocyte cells reach and kill the malignant tumor cells, so as to thereby treat the malignant tumor.--

C1 amdg 1

C2 --39.(2x amended) The method of claim 27, wherein the peptide is a fragment of an antibody.--

C2 amdg 2

C3 --41.(2X amended) The method of claim 27, wherein the peptide comprises GRGDSP (SEQ ID NO:2).--

C3 amdg 3

REMARKS

Claims 27-39 and 41 are pending. Claims 27, 39 and 41 have been amended to more particularly point out the claimed invention. Support for these amendments may be found in the specification, *inter alia*, on page 12, lines 28-31; Figures 10A and 10B; and page 8, lines 5-28. These amendments raise no issue of new

matter. Therefore, applicants request the Examiner enter these amendments.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner maintained the rejection of claim 27-38 under 35 U.S.C. §112, 2nd paragraph as set out in the previous office action. The Examiner stated that Applicant argues that "agent" is not indefinite as the specification clearly defines the term as "wherein the agent binds to a β1 integrin cell surface receptor". However, the Examiner stated that the specification at the cited section defines the antibody as being contemplated to have the specified functional limitation. The Examiner stated that the amendment to the claim still does not clarify or render definite the metes and bounds of "agent", which in a broad sense can be any molecule that will bind to the β1 integrin cell surface receptor. The Examiner stated that the "any" can include various chemical moieties (organic molecules, inorganic molecules, nucleic acids etc etc. or even peptide molecules of varied structures).

In addition, the Examiner rejected claim 41 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that claim 41 depends from a canceled claim and hence is indefinite.

Applicants' Reply

In reply, applicants traverse the rejection. Without conceding the correctness of the Examiner's position and to accelerate prosecution of the subject application, applicants have amended claim 27 to delete the term "agent" and to insert therefor the phrase "an antibody, a peptide or a peptidomimetic" in order to particularly point out the claimed subject matter. Applicants submit that the claim is clear and definite in that antibodies, peptides and peptidomimetics are definite classes of compounds. In addition, applicants have amended claim 41 to now depend from claim 27. Thus, applicants submit that the metes and bounds of the pending claims are clear.

In view of the amendments, applicants respectfully request the Examiner to reconsider and withdraw these grounds of rejection under 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner rejected claims 27-39 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an antibody and binding fragments thereof and peptide GRGDSP, does not reasonably provide enablement for any and all agents for binding to β1 integrin cell surface receptor. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The Examiner stated that the claims are drawn to a

method of treating a malignant tumour by administering an agent which binds to a β1 integrin cell surface receptor to enhance migration of leukocytes through tenascin to reach tumour cells and kill them. The Examiner stated that the specification discloses the administration of anti-β1 integrin antibodies or peptide GRGDSP were able to allow migration of leukocytes. The Examiner stated that the specification does not provide sufficient guidance as to other agents, peptidomimetics, peptides or how to begin to select the compounds to be tested. The Examiner stated that the assays may be available, but the Examiner took the position that there is no teaching provided nor working example that would lead one of skill in the art to begin to look for an "agent" which binds to β1 integrin cell surface receptor wherein it binds to that can be tested in this area as the list would be enormously long and varied. The Examiner stated that one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly claimed.

In reply, applicants traverse the rejection and submit that the claimed invention is fully enabled by the combination of what is taught by the subject application and what one of skill in the art would have known as of the effective filing date, i.e. April 22, 1996.

Applicants have amended claim 27 to be directed to a method of treating a malignant tumor in a subject wherein the malignant tumor comprises tumor cells around which tenascin has been deposited, which comprises administering to the subject an agent

that binds to a β_1 integrin cell surface receptor of leukocyte cells, wherein the agent is an antibody, a peptide or a peptidomimetic in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin so that the leukocyte cells reach and kill the malignant tumor cells, so as to thereby treat the malignant tumor.

Applicants note that the Examiner has agreed that the application fully enables an antibody and binding fragments thereof and peptide GRGDSP. The Examiner is concerned that "all agents" are not enabled. Applicants respectfully traverse this position of the Examiner, but have amended claim 27 in the interest of accelerated prosecution and without prejudice to pursue the subject matter which has been canceled in a continuation application. Applicants maintain that one of skill in the art would be able to carry out the claimed invention without undue experimentation. As of April 22, 1996, one of skill in the art would have known how to make and use peptidomimetics. See for example, U.S. Patent No. 5,331,573, Balaji, et al., issued July 19, 1994, Method of design of compounds that mimic conformational features of selected peptides. The rational design of novel compounds, useful as drugs, e.g., bioactive peptidomimetic compounds, and constrained analogs thereof, is thus made possible using the simulation methods and tools of the '573 patent.

The Examiner asserted that the specification does not provide sufficient guidance as to other agents or how to begin to select compounds to be tested. See Office Action, page 3. The

specification provides a full description of an *in vitro* assay which would enable one of skill in the art to test peptides to determine their ability to bind to a β_1 integrin cell surface receptor to enhance the migration of leukocyte cells through the tenascin. On page 15, lines 20-33, various three-dimensional matrices are described (e.g., fibrin, collagen IV ro Matrigel) which can be utilized in *in vitro* assays to test for migration of leukocyte cells in response to the presence of a particular antibody, peptide or peptidomimetic. On page 16, line 7 begins a description of the preparation of Boyden-type chemotaxis chambers which are known to one of skill in the art and are used to test the chemotaxis ability of agents such as peptides, antibodies and peptidomimetics. This chamber was used successfully to differentiate between compounds which promoted migration of cells through the three-dimensional matrix and which did not. See the Results section beginning on page 20, line 35. In addition, see the cell Migration assays described in Example 2 beginning on page 35. For example, the F(ab)'2 fragment of anti-tenascin restored PMN chemotaxis across filters coated with Matrigel and tenascin and increased cell migration. See page 40, lines 10 to 27. On the other hand, F(ab)'2 fragment of anti-proteoglycan did not reverse tenascin's inhibitiory effect on monocyte migration across filters coated with Matrigel. Therefore, the specification does indeed provide for an assay to determine which peptides, antibodies or fragments thereof or peptidomimetics would be useful in the claimed invention.

Thus, applicants submit that one of skill in the art would be able to make and use the claimed invention without undue

experimentation. Applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee is believed necessary in connection with the filing of this Amendment. If any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Jane M. Love

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents, Washington, D.C. 20231.

Jane M. Love 4/30/01

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Exhibit A - An annotated version of amended claims showing all changes relative to the previous version of that claim:

--27.(2x amended) A method of treating a malignant tumor in a subject wherein the malignant tumor comprises tumor cells around which tenascin has been deposited, [the malignant tumor being present in a subject,] which comprises administering to the subject an agent [wherein the agent] that binds to a $\hat{a}_1$ integrin cell surface receptor of leukocyte cells, wherein the agent is an antibody, a peptide or a peptidomimetic in an amount effective to inhibit [, which inhibits] signaling mediated by [a] the $\hat{a}_1$ integrin cell surface receptor [of leukocyte cells in an amount effective] and to enhance the migration of leukocyte cells through the tenascin so [as to permit] that the leukocyte cells [to] reach and kill the malignant tumor cells, so as to [and] thereby treat the malignant tumor.--

--39.(2x amended) The method of claim 27, wherein the [agent is selected from the group consisting of: a] peptide is [, a peptidomimetic, an antibody, and] a fragment of an antibody.--

--41.(2X amended) The method of claim [40] 27, wherein the peptide comprises GRGDSP (SEQ ID NO:2).--